Clinical Study Synopsis for Public Disclosure

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Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
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Name of active ingredient: Dextromethorphan hydrobromide monohydrate		**Page:** 1 of 12	**Synopsis No.:**
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Report date: 02 SEP 2010	**Trial No. / U No.:** 1134.3 / U10-2388-01	**Date of trial:** 05 JUN 2009 – 27 JUL 2009	**Date of revision :** Not applicable

Title of trial:	A phase I multiple dose trial to investigate safety with special emphasis on ECG effects and tolerability after oral doses of 30 mg qid and 90 mg qid dextromethorphan hydrobromide monohydrate (2 mg/mL syrup) in healthy male and female subjects for 2 days followed by a morning dose (extensive metabolisers of CYP 2D6) and for 10 days followed by a morning dose (poor metabolisers of CYP 2D6) (randomised, double-blind, placebo-controlled groups)
Principal Investigator:	[redacted]
Trial site:	[redacted] Germany
Publication (reference):	Data of this trial has not been published.
Clinical phase:	I
Objectives:	To investigate safety with special emphasis on electrocardiogram (ECG) effects, and tolerability of dextromethorphan hydrobromide monohydrate (2 mg/mL syrup).
Methodology:	Randomised, parallel-group, double-blind, placebo-controlled, multiple dose trial in two metaboliser groups (extensive metabolisers (EMs) and poor metabolisers (PMs) for cytochrome P (CYP) 2D6)
No. of subjects:	
planned:	Entered: 48
actual:	enrolled: 83 entered: 48 Treatment dextromethorphan syrup: entered: 32 treated: 32 analysed Treatment placebo syrup: entered: 16 treated: 16 analysed
Diagnosis and main criteria for inclusion:	Healthy male and female subjects, age ≥18 and ≤55 years, body mass index range ≥18.5 and ≤30 kg/m^2, extensive metabolisers (EMs) or poor metabolisers (PMs) for CYP 2D6

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Test product:	Dextromethorphan syrup (Bisoltussin® syrup) containing 2 mg/mL dextromethorphan hydrobromide monohydrate
dose:	30 mg qid or 90 mg qid followed by a single morning dose
mode of admin.:	Oral
batch no.:	818619 (bulk), PR08/10446 (labelled)
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Oral
batch no.:	080271 (bulk), PR08/10446 (labelled)
Duration of treatment:	Extensive CYP 2D6 metabolisers (EMs): 3 days (qid for 2 days followed by a single morning dose, both dose groups) Poor CYP 2D6 metabolisers (PMs): 11 days (qid for 10 days followed by a single morning dose, low dose group) 4 days (qid for 3 days followed by a single morning dose, high dose group)
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The following pharmacokinetic parameters were determined for dextromethorphan, dextrorphan (total and unconjugated), 3-hydroxymorphinan (total and unconjugated), and 3-methoxymorphinan After the first dose (within 5 h, before administration of the second dose): C_{max}, t_{max}, AUC_{t1-t2}, AUC_{0-5} After the second dose: $C_{max,2}$, $t_{max,2}$ After the last dose: $C_{max,N}$, $t_{max,N}$, $AUC_{t1-t2,N}$, $AUC_{0-5,N}$, $\lambda_{z,N}$, $t_{1/2,N}$, $C_{max,0-5,N}$, $t_{max,0-5,N}$, $R_{A,Cmax}$ and $R_{A,AUC0-5}$

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Safety:

Safety and tolerability were assessed based on:

- Physical examination
- Vital signs (blood pressure and pulse rate)
- 12-lead ECG including QT interval and heart rate corrected QTcF (Fridericia) and QTcB (Bazett) (according to the trial statistical analysis plan (TSAP))
- Clinical laboratory tests (clinical chemistry, haematology, urinalysis)
- Adverse events
- Assessment of tolerability by investigator

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Statistical methods:

Safety analyses were descriptive in nature.

The mean change from baseline of QTcF (Fridericia), QTcB (Bazett), uncorrected QT interval and HR was analysed in an exploratory way using an analysis of co-variance (ANCOVA) model, with the fixed effect treatment and baseline as a covariate. For the subsequent pairwise comparisons of the active treatment groups vs. placebo, two-sided 90% confidence intervals (CI) for the differences and corresponding point estimators adjusted for baseline were computed.

The change from baseline at any point was investigated using a linear mixed-effects model for repeated measures. This model included treatment as fixed effect and time as a repeated effect, the interaction effects time-by-treatment and the baseline values as a linear covariate.

The relationship between plasma concentrations and QTcF/HR change from baseline was investigated in an exploratory way using a linear mixed model approach with random intercept to estimate the QTcF/HR change from baseline and its 90% CI at the geometric mean of the C_{max} of each dose.

Descriptive statistics and tabular and graphical displays were used to summarize and evaluate the secondary pharmacokinetic parameters.

The statistical model to explore the attainment of steady state of the PMs was a repeated measures analysis of variance (ANOVA) model on the logarithmic scale including time as a repeated effect. The investigation of steady state of EMs was performed by an ANOVA including plasma concentration as a fixed effect and subject as a random effect.

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Efficacy / clinical pharmacology results:

A dose dependent exposure (C_{max} and AUC_{0-5}) to all analytes was observed after single and multiple dosing of 30 mg or 90 mg dextromethorphan qid in CYP 2D6 EMs and after a single dose of 30 mg or 90 mg dextromethorphan in CYP 2D6 PMs. Due to individual dose reductions and shortening of treatment duration in the CYP 2D6 PM planned 90 mg dose group, comparable (dextromethorphan) or even slightly lower exposure (all metabolites) was observed in comparison to the CYP 2D6 PM 30 mg dose group after multiple dosing.

The plasma concentration-time profiles and derived pharmacokinetic parameters for all analytes were markedly different between CYP 2D6 EMs and PMs. All analytes showed longer terminal half lives in PMs compared with EMs thus leading to higher accumulation of all analytes in CYP 2D6 PMs compared to EMs.

In CYP 2D6 EMs dextromethorphan was predominantly metabolised to dextrorphan and 3-hydroxymorphinan. As expected, CYP 2D6 dependent metabolism of dextromethorphan was heavily impaired in CYP 2D6 PMs. Dextromethorphan accounted for most of the exposure after single and multiple dosing in CYP 2D6 PMs. After single dose at Day 1 gMean C_{max} values of dextromethorphan were ~ 14 to ~ 21 fold higher in CYP 2D6 PMs compared to the respective dose group in CYP 2D6 EMs. After multiple dosing they were even ~ 31 to ~ 96 fold higher due to higher accumulation of dextromethorphan in CYP 2D6 PMs.

Besides dextromethorphan, 3-methoxymorphinan showed highest C_{max} values in CYP 2D6 PMs, especially pronounced after multiple dosing due to high accumulation. Highest maximum plasma concentrations of unconjugated dextrorphan, total dextrorphan, unconjugated 3-hydroxymorphinan and total 3-hydroxymorphinan were observed in CYP 2D6 EMs. In both, CYP 2D6 EMs and PMs most of dextrorphan and 3-hydroxymorphinan were present in plasma in the conjugated form as glucuronides.

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Efficacy / clinical pharmacology results:

In CYP 2D6 EMs median t_{max} values for all analytes occurred in the range of 1-3 h after drug administration of the first and second dose and after multiple dosing. In CYP 2D6 PMs median t_{max} values for all analytes except 3-methoxymorphinan occurred in the range of 1.26-5 h after drug administration of the first and second dose and after multiple dosing. 3-Methoxymorphinan median t_{max} values occurred 3-4.92 h after drug administration of the first and second dose and 2.52-8 h after multiple dosing. In CYP 2D6 PMs no sharp peak in t_{max} could be observed.

In both CYP 2D6 EM dose groups steady state for the morning dose could be reasonably assumed for all analytes at Day 2 based on visual inspection. In the CYP 2D6 PM planned 90 mg dose group, a steady state analysis was not performed since steady state was not attained due to reduced treatment duration and individual dose reductions in this treatment group. In the CYP 2D6 PM 30 mg dose group steady state for the morning dose was attained for dextromethorphan, total and unconjugated dextrorphan, as well as total and unconjugated 3-hydroxymorphinan at Day 10 the latest by visual inspection and statistical assessment. The characteristics of the predose plasma concentrations of 3-methoxymorphinan do not allow a conclusion, if steady state for the morning dose was attained.

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Safety results:

Forty-eight healthy male and female subjects were included in this trial to investigate the safety and tolerability of dextromethorphan syrup after administration of common therapeutic doses of 30 mg qid and supra-therapeutic doses of 90 mg qid. Extensive and PMs of CYP 2D6 were included in the treatment phase of this trial due to the inter-individual difference in metabolism due to the genetically polymorphic enzyme CYP 2D6.

No severe or serious adverse events were observed in this trial. Most of the adverse events reported by 35 of the 48 subjects were of mild intensity and considered to be drug-related. Other significant adverse events were observed for altogether 11 subjects. The supra-therapeutic dose of 90 mg qid was sufficiently tolerable in EMs, but not in PMs, and doses and duration of the trial were reduced for this group.

Most of the subjects reported adverse events of the MedDRA system organ classes nervous system disorders and gastrointestinal disorders.
The number of subjects with nervous system disorders or gastrointestinal disorders was higher in the PM group. There were no marked differences in frequency of subjects with diarrhoea between active treatment and placebo in both metaboliser groups.

The most frequently reported drug-related adverse events were diarrhoea, flatulence and dizziness followed by nausea, abdominal pain, headache, fatigue and paraesthesia. These events are commonly observed with the use of dextromethorphan products.

The number of subjects with nervous system disorders and gastrointestinal disorders was higher after administration of the supra-therapeutic dose (up to 90 mg dextromethorphan qid) compared to the common dose (30 mg dextromethorphan), respectively. The PMs (90 mg dextromethorphan) did not receive three times supratherapeutic doses from Day 1 evening dose on.

Psychiatric disorders were only observed in 3 subjects treated with the supratherapeutic dose; all 3 subjects were PMs.

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Safety results (continued):

In the highest dose group of PMs, the subjects were treated on a reduced dosing scheme from Day 1 evening dose on due to other significant adverse events observed on the first treatment day. At first, it was attempted to perform an individual dose titration, but as symptoms were still ongoing under reduced doses, e.g., 60 mg qid, the sponsor and the investigator decided to terminate the treatment prematurely in the highest dose group in PMs and perform the ECG and pharmacokinetic profile day already on Day 4 with a dose of 60 mg.

The investigator assessed the global tolerability as good for almost all subjects in the EM group. In the PM group, the investigator assessed the global tolerability mainly as satisfactory or good.

No clinically relevant influence of the treatment on laboratory values was observed.

Overall, the common therapeutic dose of 30 mg dextromethorphan hydrobromide monohydrate given qid for 2 days followed by a single morning dose was well tolerated by EMs of CYP 2D6. PMs did not tolerate the treatment with a clinical dose of 30 mg qid as good as the EMs, but any safety-related risks did not become evident.

The dosing scheme and time schedule of the supra-therapeutic dose had to be reduced in PMs because the supra-therapeutic dose of 90 mg qid was not sufficiently tolerated.

Increases in mean HR change from baseline compared to placebo were observed in EMs at the higher dose level, dextromethorphan 90 mg qid. They occurred at all time points on Days 1 and 3, but to a less extent on Day 3. The size of the maximal effect was around 5-7 bpm on Day 1 and 4 bpm on Day 3, respectively, with largest upper two-sided 90% confidence limits around 10 – 12 bpm on Day 1. The analyses of the relationship between HR change from baseline and the plasma concentrations yielded predicted mean values of similar size, which diminished on Day 3.

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Safety results: (continued)

In PMs, the largest effect in HR change from baseline compared to placebo, occurred on Day 1, five hours after administration of dextromethorphan 90 mg. The size of the effect was around 5 bpm with an upper two-sided 90% confidence limit of 10 bpm. On Day 4 as well as on Day 11, the differences in mean HR change compared to placebo were close to zero or below. The analyses of the relationship between HR change from baseline and the plasma concentrations yielded predicted mean values for the HR change from baseline in a range from 6 to 8 bpm on Day 1, which diminished on Days 4 and 11 for most of the analytes.

Notable findings in HR, as well as for PR and QRS interval were observed during the trial neither in PMs nor in EMs.

No subject under treatment with dextromethorphan exceeded the uncorrected QT interval threshold of 500 ms.

The analysis of the QTcF interval change from baseline demonstrated in EMs that, compared to placebo, the largest observed effect, as obtained by the repeated measures analysis, was a mean interval prolongation around 3 ms on both treatment days following administration of 30 mg qid dextromethorphan. The estimated effect at the higher dose level, 90 mg dextromethorphan, was below or close to zero on the day of first treatment as well as under steady state conditions (Day 3). The largest upper two-sided 90% confidence limits for the difference versus placebo were less than 10 ms at both dose levels and on both treatment days. The size of a maximal effect around 3 ms was also confirmed by the analyses of the relationship between QTcF interval change from baseline and the plasma concentrations of the parent compound dextromethorphan as well as its main metabolites.
Furthermore, no notable findings related to QTcF were observed at any time during the trial following administration of 30 or 90 mg dextromethorphan qid in EMs. This indicated that there was no clinically relevant increase in the QTcF interval following a 3-day administration of 30 mg and 90 mg dextromethorphan qid followed by a single morning dose compared to placebo in EMs.

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Safety results: (continued)

In PMs, the largest differences in QTcF interval duration compared to placebo were observed at both dose levels, dextromethorphan 30 and up to 90 mg qid, five hours after administration of the last morning dose (Days 4 and 11). The estimated effect sizes, obtained by the repeated measures analysis, were around 11 – 12 ms with largest upper 90% confidence limits around 17 –19 ms. The lower two-sided 90 % confidence limits at this time point ranged from 4 to 6 ms. The analyses of the relationship between plasma concentrations and QTcF interval duration yielded maximal predicted values for Day 11. The size of the maximal effect, estimated on Day 11 at the gMean C_{max} values for the lower dose group (30 mg qid), was 6 ms with an upper 90% confidence limit of 10 ms and a lower limit of 2 ms (values without placebo-adjustment). However, no notable findings were observed in PMs at any time during the trial following administration of both dose levels (30 mg/ up to 90 mg qid) of dextromethorphan. Furthermore, no subject of the PMs experienced QTcF intervals above the threshold of 450 ms or changes from baseline greater than 30 ms.

The relationship between the QTcF change from baseline and the plasma concentrations of dextromethorphan and its metabolites was also analysed using the combined data from EMs and PMs to gain precision due to an increased sample size.
For the parent compound dextromethorphan and its metabolite 3-methoxymorphinan mean QTcF changes from baseline around 5 – 6 ms with upper two-sided 90% confidence limits around 7-8 ms were predicted, whereas the predicted values for the other analytes were below 1 ms (values without placebo-adjustment). Supported also by the slope estimates, the analytes dextromethorphan and 3-methoxymorphinan were deemed to be of the most influence with regard to the observed QTcF interval prolongation. This was consistent with the pharmacokinetic results of the study showing that highest C_{max} values for dextromethorphan and 3-methoxymorphinan across all treatment groups were observed for CYP 2D6 PMs after multiple dosing at Day 4 and Day 11. However, visual inspection of the relationship of e. g. dextromethorphan and 3-methoxymorphinan shows that even in the placebo group (i. e. without drug exposure) there was a considerable scatter in the data points, and even under placebo relatively high values for QTcF prolongation compared to baseline were observed.

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Safety results (continued): Moreover, the visual inspection shows that intercepts and slopes are affected by the apparent shortening of the QTcF intervals with low plasma concentrations. Thus, the results of this analysis have to be discussed with due caution.

Conclusions: Multiple oral doses of 30 mg dextromethorphan hydrobromide monohydrate were well tolerated by EMs of CYP 2D6 administered qid for 2 days followed by a single morning dose. Multiple doses of 90 mg qid were well tolerated by most of the subjects in the EM group. The observed adverse events were mainly mild and included gastrointestinal and nervous system disorders.

PMs did not tolerate the treatment with the clinical dose of 30 mg qid as well as the EMs, but no safety-related risks became evident. The observed adverse events were of mild or moderate intensity. Most events belonged to the system organ classes gastrointestinal and nervous system disorders.

Psychiatric disorders were observed only after administration of multiple supra-therapeutic doses in the PM group.

Increases in HR change from baseline following administration of 30 mg qid and up to 90 mg dextromethorphan qid compared to placebo were observed in both metaboliser groups with largest effects on the first treatment day. However, the outlier analysis revealed no clinically relevant changes in HR, neither in EMs nor in PMs.

No clinically relevant changes following administration of 30 mg qid and up to 90 mg qid dextromethorphan were also observed in PR or QRS intervals for both metaboliser groups.

Compared to placebo, the mean QT changes from baseline following administration of 30 mg and 90 mg dextromethorphan qid were below 7 ms at all observed time points in EMs. Increases above 10 ms compared to placebo were observed in PMs on Days 4 and 11. However, no subject under treatment with dextromethorphan exceeded the uncorrected QT interval threshold of 500 ms.

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Conclusion (continued):

No clinically relevant increases in the QTcF interval change from baseline following a 2-day administration of 30 mg or 90 mg dextromethorphan qid followed by as single morning dose compared to placebo were observed in EMs. The largest upper two-sided 90% confidence limits for the difference versus placebo were less than 10 ms at both dose levels and on both treatment days.

Mean increases above 10 ms in the QTcF interval change from baseline following administration of 30 mg qid and supratherapeutic doses (intended: 90 mg qid) mg dextromethorphan compared to placebo were observed in PMs on Days 4 and 11. However, the clinical relevance of these findings in PMs remained unclear, since no subject experienced QTcF intervals above the threshold of 450 ms or changes from baseline greater than 30 ms during the trial, and the study was not designed for excluding relatively small QTcF interval changes.

The exposure-response analyses indicated a potential relationship between plasma concentrations and QTcF changes from baseline. As indicated by the highest predicted QTcF values and the slope estimates, the parent compound dextromethorphan and its metabolite 3-methoxymorphinan were deemed to be of the most influence with regard to the calculated QTcF interval prolongation. This was consistent with the pharmacokinetic results of the study, showing that highest C_{max} values for dextromethorphan and 3-methoxymorphinan across all treatment groups were observed for CYP 2D6 PMs after multiple dosing on Day 4 and Day 11. However, design limitations prevent the assessment whether this numerical QTcF interval prolongation is due to a drug effect; and the results from the ECG analysis has to be discussed with due caution.

Overall it does not seem that there is an effect tending towards QTc-prolongation in CYP 2D6 EMs. For CYP 2D6 PMs it is not possible to give any conclusion on QTc-prolongation as the data do not provide a consistent and clear picture. As inconclusive data are only seen in CYP 2D6 PMs and these subjects differ by the CYP 2D6 EMs by higher plasma concentrations of the analytes dextromethorphan and 3-methoxymorphinan, only these two analytes could be possible causes for a putative QTc-prolongation in CYP 2D6 PMs.